4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2017-N-6931]

Agency Information Collection Activities; Submission for Office of Management and Budget Review; Comment Request; Current Good Manufacturing Practices and Related Regulations for Blood and Blood Components; and Requirements for Donation Testing, Donor Notification, and "Lookback"

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA, Agency, or we) is announcing that a proposed collection of information has been submitted to the Office of Management and Budget (OMB) for review and clearance under the Paperwork Reduction Act of 1995.

DATES: Submit written comments (including recommendations) on the collection of information by **[INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].**

ADDRESSES: To ensure that comments on the information collection are received, OMB recommends that written comments be submitted to https://www.reginfo.gov/public/do/PRAMain. Find this particular information collection by selecting "Currently under Review--Open for Public Comments" or by using the search function. The OMB control number for this information collection is 0910-0116. Also, include the FDA docket number found in brackets in the heading of this document.

FOR FURTHER INFORMATION CONTACT: Amber Sanford, Office of Operations, Food and Drug Administration, Three White Flint North, 10A-12M, 11601 Landsdown St., North Bethesda, MD 20852, 301-796-8867, PRAStaff@fda.hhs.gov.

SUPPLEMENTARY INFORMATION: In compliance with 44 U.S.C. 3507, FDA has submitted the following proposed collection of information to OMB for review and clearance.

Current Good Manufacturing Practices and Related Regulations for Blood and Blood Components; and Requirements for Donation Testing, Donor Notification, and "Lookback"

OMB Control Number 0910-0116--Revision

This information collection supports Agency regulations and associated guidance. All blood and blood components introduced or delivered for introduction into interstate commerce are subject to section 351(a) of the Public Health Service Act (PHS Act) (42 U.S.C. 262(a)). Section 351(a) requires that manufacturers of biological products, which include blood and blood components intended for further manufacturing into products, have a license, issued upon a demonstration that the product is safe, pure, and potent and that the manufacturing establishment meets all applicable standards, including those prescribed in the FDA regulations designed to ensure the continued safety, purity, and potency of the product. In addition, under section 361 of the PHS Act (42 U.S.C. 264), by delegation from the Secretary of Health and Human Services, FDA may make and enforce regulations necessary to prevent the introduction, transmission, or spread of communicable diseases from foreign countries into the States or possessions, or from one State or possession into any other State or possession.

Section 351(j) of the PHS Act states that the Federal Food, Drug, and Cosmetic Act (FD&C Act) also applies to biological products. Blood and blood components for transfusion or for further manufacturing into products are drugs, as that term is defined in section 201(g)(1) of the FD&C Act (21 U.S.C. 321(g)(1)). Because blood and blood components are drugs under the FD&C Act, blood and plasma establishments must comply with the provisions and related regulatory scheme of the FD&C Act. For example, under section 501 of the FD&C Act (21 U.S.C. 351), drugs are deemed "adulterated" if the methods used in their manufacturing, processing, packing, or holding do not conform to current good manufacturing practice (CGMP) and related regulations.

The CGMP regulations (part 606) (21 CFR part 606) and related regulations implement FDA's statutory authority to ensure the safety, purity, and potency of blood and blood components. The public health objective in testing human blood donations for evidence of relevant transfusion-transmitted infections and in notifying donors is to prevent the transmission of relevant transfusion-transmitted infections. For example, the "lookback" requirements are intended to help ensure the continued safety of the blood supply by providing necessary information to consignees of blood and blood components and appropriate notification of recipients of blood components that are at increased risk for transmitting human immunodeficiency virus (HIV) or hepatitis C virus (HCV) infection.

The information collection requirements in the CGMP, donation testing, donor notification, and "lookback" regulations provide FDA with the necessary information to perform its duty to ensure the safety, purity, and potency of blood and blood components. These requirements establish accountability and traceability in the processing and handling of blood and blood components and enable FDA to perform meaningful inspections.

The recordkeeping requirements serve preventive and remedial purposes. The third-party disclosure requirements identify various blood and blood components and important properties of the product, demonstrate that the CGMP requirements have been met, and facilitate the tracing of a product back to its original source. The reporting requirements inform FDA's Center for Biologics Evaluation and Research of certain information that may require immediate corrective action.

Respondents to this collection of information are licensed and unlicensed blood establishments that collect blood and blood components, including Source Plasma and Source Leukocytes, inspected by FDA, and transfusion services inspected by Centers for Medicare and Medicaid Services (CMS). Based on submission data, there are approximately 864 licensed Source Plasma establishments and approximately 1,789 licensed blood collection establishments, for an estimated total of 2,653 (864 + 1,789) licensed blood collection establishments. Also,

there are an estimated total of 817 unlicensed, registered blood collection establishments for an approximate total of 3,470 collection establishments (864 + 1,789 + 817 = 3,470 establishments). Of these establishments, approximately 856 perform plateletpheresis (777) and leukapheresis (79). These establishments annually collect approximately 73.7 million units of Whole Blood and blood components, including Source Plasma and Source Leukocytes, and are required to follow FDA "lookback" procedures. In addition, there are another estimated 4,961 establishments that fall under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) (formerly referred to as facilities approved for Medicare reimbursement) that transfuse blood and blood components.

The following reporting and recordkeeping estimates are based on information provided by industry, CMS, and our experience with the information collection. We estimate 53.5 million donations of Source Plasma from approximately 2.5 million donors and estimate 12.3 million donations of Whole Blood and apheresis Red Blood Cells, including an estimated 10,000 (approximately 0.081 percent of 12.3 million) autologous donations, from 9 million donors. Assuming each autologous donor makes an average of 1.1 donations, we estimate there are 9,090 autologous donors (10,000 autologous/1.1 average donations).

We estimate 0.53 percent (56,000 ÷ 10,654,000) of the 77,000 donations that are donated specifically for the use of an identified recipient would be tested under the dedicated donors' testing provisions in § 610.40(c)(1)(ii) (21 CFR 610.40(c)(1)(ii)).

Under § 610.40(g)(2) and (h)(2)(ii)(A), Source Leukocytes, a licensed product that is used in the manufacture of interferon, which requires rapid preparation from blood, is currently shipped prior to completion of testing for evidence of relevant transfusion-transmitted infections. Shipments of Source Leukocytes are approved under a biologics license application and each shipment does not have to be reported to the Agency. Based on a review of data, FDA receives less than one application per year from manufacturers of Source Leukocytes; however, we estimate one annually for this analysis.

Also according to Agency data, there are approximately 15 licensed manufacturers that ship known reactive human blood or blood components under § 610.40(h)(2)(ii)(C) and (D). We estimate each manufacturer would ship an average of 1 unit of human blood or blood components per month (12 per year) that would require two labels: one as reactive for the appropriate screening test under § 610.40(h)(2)(ii)(C) and the other stating the exempted use specifically approved by FDA under § 610.40(h)(2)(ii)(D).

Based on information received from industry, we estimate 7,500 donations that test reactive by a screening test for syphilis and are determined to be biological false positives by additional testing annually. These units would be labeled according to § 610.40(h)(2)(vi).

Human blood or a blood component with a reactive screening test, as a component of a medical device, is an integral part of the medical device; e.g., a positive control for an in vitro diagnostic testing kit. It is the usual and customary business practice for manufacturers to include on the container label a warning statement indicating that the product was manufactured from a donation found to be reactive for the identified relevant transfusion-transmitted infection(s). In addition, on the rare occasion when a human blood or blood component with a reactive screening test is the only component available for a medical device that does not require a reactive component, then a warning statement must be affixed to the medical device. To account for this rare occasion under § 610.42(a) (21 CFR 610.42(a)), we estimate that the warning statement would be necessary no more than once a year.

We estimate 3,100 repeat donors will test reactive on a screening test for HIV. We assume an average of three components was made from each donation. Under § 610.46(a)(1)(ii)(B) and (a)(3) (21 CFR 610.46(a)(1)(ii)(B) and (b)(3)), this estimate results in 9,300 (3,100 × 3) notifications of the HIV screening test results to consignees by collecting establishments for the purpose of quarantining affected blood and blood components, and another 9,300 (3,100 × 3) notifications to consignees of subsequent test results.

We estimate 4,961 consignees will be required under § 610.46(b)(3) to notify transfusion recipients, their legal representatives, or physicians of record an average of 0.35 times per year resulting in a total number of 1,755 (585 confirmed positive repeat donors × 3) notifications. Also, under § 610.46(b)(3), we estimate and include the time to gather test results and records for each recipient and to accommodate multiple attempts to contact the recipient.

Furthermore, we estimate 6,800 repeat donors per year would test reactive for antibody to HCV. Under §§ 610.47(a)(1)(ii)(B) and (a)(3) (21 CFR 610.47(a)(1)(ii)(B) and (a)(3)), collecting establishments would notify the consignee two times for each of the 20,400 (6,800 × 3 components) components prepared from these donations: once for quarantine purposes and again with additional HCV test results for a total of 40,800 (2 × 20,400) notifications as an annual ongoing burden. Under § 610.47(b)(3), we assume 4,961 consignees notify approximately 2,050 recipients or their physicians of record annually.

Based on industry estimates, approximately 18.15 percent of approximately 14,018,000 million potential donors (2,544,000 donors) who come to donate annually are determined not to be eligible for donation prior to collection because of failure to satisfy eligibility criteria. It is the usual and customary business practice of approximately 2,606 (1,789 + 817) blood collecting establishments to notify onsite and to explain why the donor is determined not to be suitable for donating. Based on such available information, we estimate that two-thirds (1,737) of the 2,606 blood collecting establishments provided onsite additional information and counseling to a donor determined not to be eligible for donation as usual and customary business practice. Consequently, we estimate one-third, or 869 of the 2,606 blood collecting establishments, would need to provide, under § 630.40(a) (21 CFR 630.40(a)), additional information and onsite counseling to the estimated 848,000 (one-third of approximately 2,544,000) ineligible donors.

We estimate another 0.6 percent of 14,018,000 potential donors (84,108 donors) are deferred annually based on test results. We assume 95 percent of the establishments that collect 99 percent of the blood and blood components notify donors who have reactive test results for

HIV, Hepatitis B Virus, HCV, Human T-Lymphotropic Virus, and syphilis as their usual and customary business practice. Consequently, 5 percent of the 2,653 licensed establishments (133) collecting 1 percent (841) of the deferred donors (84,108) would notify donors under § 630.40(a).

As part of their usual and customary business practice, collecting establishments notify an autologous donor's referring physician of reactive test results obtained during the donation process required under § 630.40(d)(1). However, we assume 5 percent of the 1,789 blood collection establishments (89) may not notify the referring physicians of the estimated 2 percent of 10,000 autologous donors with the initial reactive test results (200) as their usual and customary business practice.

We assume 95 percent of recordkeepers, which account for 99 percent of blood donations, have developed standard operating procedures (SOPs) as part of their customary and usual business practice. Establishments may minimize burdens associated with CGMP and related regulations by using model standards developed by industries' accreditation organizations. These accreditation organizations represent almost all registered blood establishments.

Under § 606.160(b)(1)(ix) (21 CFR 606.160(b)(1)(ix)), we assume a total number of annual records based on 2,544,000 ineligible donors and each of the estimated 2,628,108 (2,544,000 + 84,108) donors deferred based on reactive test results for evidence of infection because of relevant transfusion-transmitted infections. Under § 606.160(b)(1)(xi), only the 1,789 registered blood establishments collect autologous donations and, therefore, are required to notify referring physicians. We estimate that 4.5 percent of the 9,090 autologous donors (409) will be deferred under § 610.41 (21 CFR 610.41), which in turn will lead to the notification of their referring physicians.

Under § 610.41(b), we estimate 25 submissions for requalification of donors each requiring 7 hours per submission. In addition, we assume that there would be only three

notifications for requalification of donors under § 630.35(b) (21 CFR 630.35(b)), which would also require 7 hours for each submission.

FDA permits the shipment of untested or incompletely tested human blood or blood components in rare medical emergencies and when appropriately documented (§ 610.40(g)(1)). We estimate the recordkeeping under § 610.40(g)(1) to be minimal with one or fewer occurrences per year. The reporting of test results to the consignee in § 610.40(g) is part of the usual and customary business practice of blood establishments.

In the *Federal Register* of February 22, 2021 (86 FR 10582), we published a 60-day notice requesting public comment on the proposed collection of information. No comments were received. On our own initiative, however, and for efficiency of Agency operations, we are revising the information collection to include and consolidate related information collection found in Agency guidance. The guidance documents were issued consistent with our good guidance practice regulations in 21 CFR 10.115, which provide for public comment at any time.

We are revising the information collection to reference the Agency guidance document entitled "Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion" (December 2020), which provides blood collection establishments and transfusion services with recommendations to control the risk of bacterial contamination of room temperature stored platelets intended for transfusion. The guidance is available for download from our website at: https://www.fda.gov/media/123448/download.

The guidance recommends blood collection establishments notify transfusion services if a distributed platelet product is subsequently identified as positive for bacterial contamination and that blood establishments communicate to their consignees the type of storage container the platelets are stored in. We assume such notification is a usual and customary business practice for blood establishments and, therefore, estimate no burden estimate for the information collection.

We also developed the guidance entitled "Labeling of Red Blood Cell Units with Historical Antigen Typing Results" (December 2018) to provide establishments that collect blood and blood components for transfusion with recommendations for labeling Red Blood Cell units with non-ABO/Rh(D) antigen typing results obtained from previous donations (historical antigen typing results). The guidance is available for download from our website at: https://www.fda.gov/media/119376/download.

The guidance recommends disclosing non-ABO/Rh(D) historical antigen typing results on a tie-tag or directly on the container label. We assume such information disclosures would be usual and customary for blood establishments and, therefore, estimate no burden for the information collection, currently approved under OMB control number 0910-0862.

We estimate the burden of this collection of information as follows:

Table 1.--Estimated Annual Reporting Burden[1]

21 CFR Section; Activity	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
606.170(b)[2]; Donor or recipient fatality reporting	81	1	81	20	1,620
610.40(g)(2); Application for approval to ship	1	1	1	1	1
610.41(b); Request for requalification of donor	2,653	0.0094	25	7	175
610.40(h)(2)(ii)(A); Application for approval for shipment or use	1	1	1	1	1
630.35(b); Request for requalification of donor	2,653	0.00113	3	7	21
Total					1,818

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.
[2] The reporting requirement in § 640.73, which addresses the reporting of fatal donor reactions, is included in the estimate for § 606.170(b).

Table 2.--Estimated Annual Recordkeeping Burden[1]

21 CFR Section; Activity	No. of Recordkeepers	No. of Records per Recordkeeper	Total Annual Records	Average Burden per Recordkeeping	Total Hours
606.100(b)[2]; Maintenance of SOPs	422[5]	1	422	24	10,128
606.100(c); Records of investigations	422[5]	10	4,220	1	4,220
606.110(a)[3]; Documentation donor's health permits plateletpheresis or leukapheresis	43[6]	1	43	0.5 (30 minutes)	22
606.151(e); Records of emergency transfusions	422[5]	12	5,064	0.08 (5 minutes)	405
606.160[4]; Records of collection, processing, compatibility testing, storage, and distribution of each	422[5]	907.583	383,000	0.75 (45 minutes)	287,250

unit of blood and blood components					
606.160(b)(1)(viii); HIV consignee notification	1,789 4,961	10.4533 3.6537	18,701 18,126	0.17 (10 minutes) 0.17 (10 minutes)	3,179 3,081
606.160(b)(1)(viii); HCV consignee notification	1,789 4,961	22.8060 8.2241	40,800 40,800	0.17 (10 minutes) 0.17 (10 minutes)	6,936 6,936
HIV recipient notification	4,961	0.3538	1,755	0.17 (10 minutes)	298
HCV recipient notification	4,961	0.4132	2,050	0.17 (10 minutes)	349
606.160(b)(1)(ix); Donor notification records	3,470	757.380	2,628,109	0.05 (3 minutes)	131,405
606.160(b)(1)(xi); Physician notification records	1,789	0.2286	409	0.05 (3 minutes)	20.5
606.165; Distribution and receipt records	422[5]	907.583	383,000	0.08 (5 minutes)	30,640
606.170(a); Adverse reaction records	422[5]	12	5,064	1	5,064
610.40(g)(1); Documentation of medical emergency	3,470	1	3,470	0.5 (30 minutes)	1,735
630.15(a)(1)(ii)(B); Documentation required for dedicated donation	1,789	1	1,789	1	1,789
630.20(c); Documentation of exceptional medical need	1,789	1	1,789	1	1,789
Total					495,247

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.
[2] The recordkeeping requirements in §§ 606.171, 630.5(d), 630.10(c)(1) and (2), and 640.66, which address the maintenance of SOPs, are included in the estimate for § 606.100(b).
[3] The recordkeeping requirements in § 640.27(b), which address the maintenance of donor health records for the plateletpheresis, are included in the estimate for § 606.110(a).
[4] The recordkeeping requirements in §§ 606.110(a)(2), 630.5(b)(1)(i), 630.10(f)(2) and (4), 630.10(g)(2)(i), 630.15(a)(1)(ii)(A) and (B), 630.15(b)(2), (b)(7)(i) and (iii), 630.20(a) and (b), 640.21(e)(4), 640.25(b)(4) and (c)(1), 640.31(b), 640.33(b), 640.51(b), 640.53(b) and (c), 640.56(b) and (d), 630.15(b)(2), 640.65(b)(2)(i), 640.65(b)(2)(i), 640.71(b)(1), 640.72, 640.73, and 640.76(a) and (b), which address the maintenance of various records are included in the estimate for § 606.160.
[5] Five percent of establishments that fall under CLIA that transfuse blood and components and FDA-registered blood establishments (0.05 × 4,961 + 3,470 = 422).
[6] Five percent of plateletpheresis and leukapheresis establishments (0.05 × 856 = 43).

Table 3.--Estimated Annual Third-Party Disclosure Burden[1]

21 CFR Section; Activity	No. of Respondents	No. of Disclosures per Respondent	Total Annual Disclosures	Average Burden per Disclosure	Total Hours
606.145(c); Notification of bacterial contamination of platelets	4,961	0.2822	1,400	0.02 (90 seconds)	28
606.170(a); Reports of transfusion reaction	422[2]	12	5,064	0.5 (30 minutes)	2,532
610.40(c)(1)(ii); Labeling of donation dedicated to single recipient	3,470	0.0395	137	0.08 (5 minutes)	11
610.40(h)(2)(ii)(C) and (D); Labeling of reactive blood and blood components	15	12	180	0.2 (12 minutes)	36

610.40(h)(2)(vi); Labeling of reactive blood and blood components	3,470	2.1614	7,500	0.08 (5 minutes)	600
610.42(a); Warning statement for medical devices	1	1	1	1	1
610.46(a)(1)(ii)(B); Notification to consignees to quarantine (HIV "lookback")	1,789	5.1984	9,300	0.17 (10 minutes)	1,581
610.46(a)(3); Notification to consignees of further testing	1,789	5.1984	9,300	0.17 (10 minutes)	1,581
610.46(b)(3); Notification to recipients	4,961	0.3528	1,750	1	1,750
610.47(a)(1)(ii)(B); Notification to consignees to quarantine (HCV "lookback")	1,789	11.4030	20,400	0.17 (10 minutes)	3,468
610.47(a)(3); Notification to consignees of further testing	1,789	11.4030	20,400	0.17 (10 minutes)	3,468
610.47(b)(3); Notification to recipients	4,961	0.4132	2,050	1	2,050
630.40(a); Notification of donors determined not to be eligible for donation	869	975.834	848,000	0.08 (5 minutes)	67,840
630.40(a); Notification of donors deferred based on reactive test results	133	6.323	841	1.5	1,262
630.40(d)(1); Notification to physician of autologous donor	89	2.247	200	1	200
Total					86,408

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.
[2] Five percent of establishments that fall under CLIA that transfuse blood and components and FDA-registered blood establishments (0.05 × 4,961 + 3,470 = 422).

We have adjusted our burden estimate for this information collection since last OMB review to reflect an overall increase of 79,024 hours annually. We attribute this adjustment to an increase in the number of registered blood establishments over the last 3 years.

Dated: June 21, 2021.

Lauren K. Roth,

Acting Principal Associate Commissioner for Policy.

[FR Doc. 2021-13575 Filed: 6/24/2021 8:45 am; Publication Date: 6/25/2021]